International Journal of Laboratory Hematology
The Official journal of the International Society for Laboratory Hematology

REVIEW INTERNATIONAL JOURNAL OF LABORATORY HEMATOLOGY

Diagnosis and treatment of disseminated intravascular coagulation

M. LEVI

Department of Vascular Medicine, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands

Correspondence:
Marcel Levi, Department of Vascular Medicine, Academic Medical Centre E-2, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands.
Tel.: (31) 20 5662109;
Fax: (31) 20 6212796;
E-mail: m.m.levi@amc.uva.nl

doi:10.1111/ijlh.12221

Received 28 December 2013; accepted for publication 28

Keywords
Disseminated intravascular coagulation, platelets, coagulation factors, fibrin degradation products, tissue factor, antithrombin, activated protein C, thrombomodulin

SUMMARY

Disseminated intravascular coagulation (DIC) is a condition in which systemic activation of coagulation without a specific localization occurs, resulting in extensive formation of intravascular fibrin, particularly in small and midsize vessels. Disseminated intravascular coagulation may lead to several altered coagulation parameters, including a low platelet count, abnormal global clotting assays, low levels of physiological anticoagulant proteases, or increased fibrin degradation products. Also, more complex assays for activation of coagulation factors or pathways may indicate involvement of these molecules in DIC. None of these tests alone, however, can accurately ascertain or rebuff a diagnosis of DIC. Nonetheless, a combination of readily available routine assays may be instrumental in establishing a diagnosis of DIC and can also be useful to point to a subset of patients with DIC that may need definite, often costly, interventions in the hemostatic system. Current insights on relevant etiological pathways that may contribute to the occurrence of DIC have led to innovative therapeutic and adjunctive approaches to patient with DIC. Management options directed at the amelioration of hemostatic activation may tentatively be indicated and were found to be advantageous in experimental and clinical investigations. These treatments encompass elimination of tissue factor-mediated thrombin generation or restitution of normal anticoagulant function.

INTRODUCTION

Disseminated intravascular coagulation (DIC) is an intense manifestation of hemostatic activation that may occur in a variety of clinical settings, most of which imply some degree of local or widespread inflammation. Activation of coagulation in the systemic circulation, inefficiently counteracted by coagulation inhibitors and amplified by decreased physiological fibrin-degrading potential, may result in fibrin formation in small and midsize vessels and microvascular thrombotic microangiopathy [1]. The substantial and continuing thrombin generation may result in exhaustion of coagulation proteases and platelets, leading to an increased risk of serious hemorrhagic complications, which sometimes may be the most impressive clinical presentation. Currently, most etiological factors in DIC have been identified, which may lead to a more accurate diagnosis of the disorder. Nevertheless, the precise diagnosis of DIC may be tricky, as most assays demonstrate exhaustion of coagulation proteases or indicate thrombocytopenia, while biomarkers that indicate specific activation of a coagulation factor or pathway are mostly inaccurate and are often not accessible in most hospitals on a 24 h basis [2, 3]. In this overview, we will discuss both widely available and more complex laboratory assays that may be helpful in the diagnosis of DIC.

With growing understanding that the simultaneous activation of systemic inflammatory activity and activation of hemostasis may lead to organ failure in critically ill patients, the adjunctive management of DIC has been intensely studied recently [4]. Current thinking about the pathophysiology of DIC has resulted in novel strategies directed at inhibiting the initiation or propagation of fibrin formation. The most important therapeutic options will be reviewed in this study.

LABORATORY FINDINGS IN DIC

Platelets

Low platelets or a rapidly developing thrombocytopenia is a central characteristic of DIC (Table 1). As a platelet count of <150 × 10^9/L in intensive care patients frequently occurs [5, 6], a low platelet count is not a specific feature of DIC. Moderate-to-severe thrombocytopenia (platelets <100 × 10^9/L) is observed in the majority of patients with DIC, whereas a smaller proportion of patients (about 10–15%) have severe thrombocytopenia (<50 × 10^9/L). In critically ill postoperative patients with DIC, thrombocytopenia (<100 × 10^9/L platelets) occurs in >80% [7]. The importance of a low platelet count in DIC is associated with an increased risk of hemorrhagic complications, especially patients with a thrombocytopenia of <50 × 10^9/L have a fourfold to fivefold increased risk for hemorrhage in comparison with patients with normal platelet numbers, above all when the patient uses antithrombotic agents [5]. The risk of intracranial hemorrhage in patients with DIC is relatively modest (0.3–0.5%), but more than 85% of patients with DIC with this event, a moderate or severe thrombocytopenia (<100 × 10^9/L) is present. In spite of the origin, a low platelet count is an independent prognostic factor in ICU survival with a relative risk of 2–4 in various investigations [5], especially, a sustained low platelet count during more than 4 days after admission to a critical care department or a worsening thrombocytopenia during admission of a critically ill patient is related to a fivefold increased risk of death [5, 8].

Table 1. Routine laboratory value abnormalities in DIC

Test	Abnormality	Causes other than DIC contributing to test result
Platelet count	Decreased	Sepsis, impaired production, major blood loss, hypersplenism
Prothrombin time	Prolonged	Vitamin K deficiency, liver failure, major blood loss
aPTT	Prolonged	Liver failure, heparin treatment, major blood loss
Fibrin degradation products	Increased	Hematoma
Protease inhibitors*	Decreased	Liver failure, capillary leakage

*e.g., protein C, AT, protein S.

Coagulation factors and global clotting times

Ongoing activation and subsequent exhaustion of coagulation proteases results in decreased concentrations of these factors in patients with DIC (Table 1). Also, reduced production of clotting factors, caused by attenuated liver function and/or shortage of vitamin K, and simultaneous coagulation factor reductions, due to substantial hemorrhage, may be important in DIC (Table 2) [9]. Despite the fact that the preciseness of one-stage clotting measurements in consumption coagulopathies has been debated (due to interference with activated coagulation factors in the assay), the concentration of clotting factors seems to show a fairly good relationship with the intensity of DIC. The reduced level of clotting factors is readily detected by abnormal coagulation screening tests, including the prothrombin time (PT) or the activated partial thromboplastin time (aPTT). An abnormal PT or aPTT can be found in 15–30% of critically ill patients and

Table 2. Differential diagnosis of suspected DIC

Differential diagnosis	Additional diagnostic clues
DIC	Prolonged aPTT and PT, increased fibrin split products, low levels of physiological anticoagulant factors (antithrombin, protein C)
Massive blood loss	Major bleeding, low hemoglobin, prolonged aPTT and PT,
Thrombotic microangiopathy	Schistocytes in blood smear, Coombs-negative hemolysis, fever, neurologic symptoms, renal insufficiency, coagulation times usually normal, ADAMTS13 levels decreased; PT and aPTT normal
Heparin-induced thrombocytopenia	Use of heparin, venous or arterial thrombosis, positive HIT test (usually ELISA for heparin-platelet factor IV antibodies), rebound of platelets after cessation of heparin; coagulation times usually normal; PT normal (aPTT may be prolonged due to heparin)
Vitamin K deficiency	PT prolonged, aPTT normal or slightly prolonged, normal platelet count
Liver insufficiency	PT and aPTT prolonged, platelets (moderately) low, liver test abnormalities, hypersplenism, jaundice

occurs in the vast majority of patients with DIC [10]. However, it should be mentioned that overall clotting assays, such as the PT and aPTT, not very well mirror *in vivo* coagulation. Nevertheless, these assays are a readily available means to swiftly assess the level of one or more clotting factors [11]. Usually, global clotting assays will become abnormal if the concentration of clotting proteins is <50% and for some reagents only <30–40%. This is important because the concentrations of clotting factors, that are required for correct functioning of coagulation, are approximately in the range of 25–50%. Various reagents may produce highly variable normal values and abnormal levels. Because of this, a growing number of laboratories are employing the international normalized ratio (INR) as a substitute of the PT. The advantage of enhanced comparability between centers, however, should be offset against the fact that the INR has not been developed as a screening test for clotting abnormalities [12, 13].

In contradiction to most other coagulation factors, plasma concentrations of factor VIII are markedly increased in most patients with DIC, presumably caused by substantial release of von Willebrand factor from vascular endothelial cells and acute phase properties of factor VIII. Previous investigations have directed at a relative deficiency of the von Willebrand factor cleaving protease ADAMTS-13, which may result in increased levels of very large von Willebrand multimers in plasma, promoting platelet-vessel wall binding and the ensuing occurrence of a thrombotic microangiopathic condition, which may also be a factor in organ failure [14].

In older literature, assessment of fibrinogen is often mentioned as a valuable assay to ascertain the presence of DIC; however, this marker is not useful to establish DIC in the vast majority of patients. Fibrinogen behaves as an acute phase protein, and therefore, its concentration can be completely normal for a long time despite massive consumption levels. The accuracy of a low fibrinogen concentration in case of DIC was <30%, and low levels of fibrinogen were only established in patients with very serious consumption coagulopathies [15].

Markers for fibrin formation and degradation

Assessment of soluble fibrin or fibrin fragments in blood can be useful to establish intravascular fibrin formation in DIC. Previous investigations have indicated that if the level of soluble fibrin was sufficiently high, a diagnosis of DIC could be ascertained [16, 17]. In the last 10 years, novel assays have become available that are capable of quantitating soluble fibrin in blood and these tests have been studied for their utility in making a diagnosis of DIC [18, 19]. Theoretically, soluble fibrin in blood can only result from intravascular fibrin formation, and this assay will not be affected by generation of fibrin outside the vasculature, as may be present during inflammation or injuries.

Alternative assays that are commonly employed assess increased fibrin degradation products. Fibrin degradation products are present in >40% of critically ill patients, in 80% of patients with trauma and in virtually all patients with systemic inflammatory response syndromes and associated consumption coagulopathy [20, 21]. Fibrin split products may be detected by specific immunoassays or by latex agglutination tests, facilitating a swift point of care assessment in urgent situations. A disadvantage of the currently used tests for fibrin split products is that the assays do not distinguish products of degraded cross-linked fibrin from fibrinogen degradation, and this may produce falsely abnormal results [22]. As a result, the specificity of increased levels of fibrin split products is not very high and these high levels may occur in a myriad of other situations, such as in postoperative patients, patients with major injuries, systemic infectious, or inflammatory states or thrombo-embolic disease. As fibrin split products are processed by the liver and released by the kidneys, levels of fibrin degradation products are affected by liver and renal function. New generation fibrin split product assays are more precisely directed against specific neo-epitopes on degraded cross-linked fibrin. An example of these assays is the test assessing fragment D-dimer, which measures the presence of the plasmin-degraded cross-linked γ-chain of fibrin. These assays probably more accurately distinguish degradation of cross-linked fibrin from degraded fibrinogen [20]. D-dimer concentrations are increased in patients with DIC, but for example cannot discriminate patients with consumption coagulopathy from patients with venous thrombosis or pulmonary embolism, or postoperative patients.

Natural anticoagulants

Assessment of the activity of physiological anticoagulant pathways, such as the antithrombin system or the activated protein C system, may provide useful biomarkers for an ongoing consumption coagulopathy. Reduced concentrations of antithrombin or protein C can be detected in about 50% of ICU patients and in 90% of patients with DIC [21, 23]. Antithrombin is the most important regulator of thrombin activity and may be quickly depleted during sustained generation of thrombin. Concentrations of antithrombin have been demonstrated to be strongly correlated with mortality in critically ill patients with DIC. The reasons for the reduction in antithrombin levels are ongoing consumption, reduced production (due to a negative acute phase response), and neutrophilic elastase-mediated breakdown of the protease inhibitor [24]. Impaired glycosaminoglycan presence at the vascular wall surface caused by the effect of inflammatory mediators on production by the endothelium may also play a role, as glycosaminoglycans may serve as natural heparin-like binders to antithrombin, inducing a conformational transformation of the antithrombin molecule. This may lead to different kinetics of antithrombin binding to thrombin, making antithrombin from a relatively inefficient to a highly effective regulator of thrombin activity.

A low concentration of protein C may also be regarded as a marker for the intensity of the consumption coagulopathy. Sepsis with *Neisseria meningitides* results in extremely reduced levels of protein C, which is a crucial factor in dedevelopment of purpura fulminans [25]. Impairment of endothelial cell function is another pathway leading to reduced activity of the protein C system in patients with consumption coagulopathies. Normally, protein C is activated by thrombomodulin at the endothelial surface after activation by thrombin. The thrombin to thrombomodulin binding not only leads to an approximate 100-fold intensification of protein C activation, but also serves as a scavenging function for free thrombin thereby impeding the generation of fibrin and reaction of thrombin with cellular receptors on various vascular and circulating cells. Lastly, thrombomodulin affects fibrinolysis by amplifying the activation of plasma carboxypeptidase thrombin-activatable fibrinolysis inhibitor (TAFI) [26]. Interaction of protein C with the endothelial protein C receptor (EPCR) leads to a substantial increase in the activation of protein C [27]. The protein C system is seriously impaired during systemic inflammatory states, which is caused to markedly decrease expression of thrombomodulin on the vessel wall, as has also been confirmed *in vivo* in skin biopsies from with Gram-negative sepsis [28] Reduced concentrations of the cofactor protein S may further diminish the activity of the protein C system. Some studies have suggested that inherited thrombophilia may influence the incidence and severity of consumption coagulopathies but this has been debated by other observations [29].

Lastly, another regulatory system to control activation of coagulation is the activity of tissue factor pathway inhibitor (TFPI), the main regulator of the tissue factor–factor VIIa complex. Tissue factor pathway inhibitor is a Kunitz-type anticoagulant protein, which interacts with tissue factor bound to factor VIIa and factor Xa. However, the precise function of TFPI in the control of coagulation activation secondary to inflammation has not yet been elucidated in full detail. Plasma concentrations of TFPI in patients with consumption coagulopathies are often moderately reduced [30]. Experimental and clinical evidence, however, points to the notion that the endogenous level of TFPI is probably inadequate to control thrombin generation in DIC [31].

Clot dissolution

In the early phase of DIC, an increase in plasminogen activators, in particular tissue-type plasminogen activator (t-PA) and urokinase-type plasminogen activator (u-PA), results from release from perturbed endothelial cells and leads to plasmin generation. Soon hereafter, this plasmin generation is shut off by a long-lasting enhancement of plasma levels of plasminogen activator inhibitor, type 1 (PAI-1) [32]. In patients with severe consumptive coagulopathies, this dynamic response in fibrinolysis can be detected by different assays. Concentrations of fibrin split products, as discussed earlier, may ideally be regarded as marker of endogenous fibrinolysis but are in reality most strongly associated with coagulation activation. Fibrinolytic activity may be quantitated by assessment of plasma concentrations of plasminogen and its inhibitor α2-antiplasmin. Decreased concentrations may reflect exhaustion of these factors. The measurement of α_2-antiplasmin concentrations may be most useful to assess the dynamics of fibrinolytic activation because of the relatively low concentration of this inhibitor in plasma and its high affinity for plasmin. As levels of α2-antiplasmin fall, alternative protease inhibitors, including antithrombin, α2-macroglobulin, α1-antitrypsin, and C1-inhibitor can also become effective inhibitors of plasmin [33]. Direct assessment of plasmin generation can be made by assaying plasmin-α2-antiplasmin (PAP) complexes, which are indeed increased in patients with consumptive coagulopathies [34]. The fibrinolytic shutdown in patients with DIC due to increased levels of plasminogen activator inhibitor type I (PAI-1) can be assessed through measurement of this protein. Increased concentrations of PAI-1 are markedly associated with high mortality in patients with DIC [35]. Several investigations have demonstrated that a polymorphism in the PAI-1 gene, the 4G/5G mutation, affects plasma concentrations of PAI-1, but can be connected to the clinical course of patients with severe sepsis and secondary coagulopathy. Presence of the 4G/4G genotype was associated with considerably higher PAI-1 levels in blood and excess mortality [36].

Molecular biomarkers of DIC

The extent of the derangement of coagulation in patients with DIC can be evaluated by measuring molecular biomarkers that are liberated upon the conversion of a coagulation zymogen to an active factor. Often employed markers are the prothrombin activation peptide F1+2 (F1+2), or the small peptides that are released upon activation of factors IX or X [22]. Plasma concentrations of these peptides are significantly increased in patients with DIC. Increased levels of complexes between thrombin-and antithrombin may provide insight into the extent of prothrombin to thrombin conversion as well. In addition, fibrin generation can be assessed by measuring concentrations of fibrinogen activation fragment fibrinopeptide-A (FPA) [37]. These molecular biomarkers may detect even minimal hemostatic activation and are highly sensitive in DIC. However, their overall accuracy as a diagnostic test for DIC is presumably modest as most situations leading to critical illness will result in vastly increased concentrations of these biomarkers. Another practical drawback of these assays is that they are not readily available in most centers, so that their use is restricted to research settings. Hence, despite the fact that these assays may be helpful for a better understanding of pathogenetic pathways leading to DIC or the evaluation of new therapeutic interventions, their application in routine clinical practice is quite modest so far.

Bedside tests

Thromboelastography (TEG) is a technique that has been around for many years but that has gained considerable renewed attention recently due to automation and commercial employment. Contemporary versions, for example rotational thrombelastography (ROTEM) are increasingly employed in critically ill patients, including those with DIC [38]. The benefit of

TEG compared with usual coagulation parameters is that it includes an assessment of platelet function and of clot-dissolving potential. Procoagulant as well as anticoagulant states as indicated with TEG was demonstrated to have a good correlation with clinically important organ dysfunction and survival [39, 40], although its advantage over usual coagulation assays has not yet been confirmed [41]. Also, thrombelastography seems to be excessively susceptible to distinct hemostatic interventions, such as infusion of fibrinogen concentrate, of which the therapeutic advantage has not been equivocally demonstrated. The accurate use of TEG for the diagnosis of DIC has not been rigorously evaluated although supporters believe that the assay may be helpful for appraising the state of coagulation in patients with critical illness.

Composite diagnostic systems for DIC

Based on retrospective analyses of series of patients with DIC composite scores for the diagnosis of this coagulopathy have been devised by the International Society on Thrombosis and Hemostasis (ISTH) [42]. The system is based on readily available laboratory tests, that is, platelet count, PT, a fibrin degradation product (such as D-dimer), and fibrinogen levels. A diagnosis of DIC can be made when there are five or more points, while lower scores are suggestive of non-overt DIC. For less severe manifestations of DIC, a more complex composite score has been proposed, which awaits validation [43]. The PT expressed in seconds in the scoring system may be replaced by the INR, making consistency between centers and standardization easier [44]. The best threshold value for the fibrin-related marker was assessed, thereby improving the accuracy of the system [45]. Validation analyses confirm a high accuracy of the scoring system for the diagnosis of DIC [15, 46]. As most patients in the validation studies had sepsis, specific analyses of series of patients with distinct causal conditions causing DIC (e.g., patients with malignancy or patients with peri-partum calamities) demonstrate analogous results [47, 48]. The intensity of the coagulopathy as judged by this composite score is strongly associated with survival rates in critically ill patients [49]. Combining predictive intensive care measurement systems such as Acute Physiology and Chronic Health Evaluation (APACHE-II) with the DIC score seems to be a potent method to predict the prognosis in DIC. Similar composite scores have been designed and studied in Japan [50]. The most important discrepancy between the ISTH and Japanese scores is a higher proportion of patients with haemato-oncological diseases that are diagnosed with DIC by the Japanese systems.

Dynamic coagulation monitoring in DIC

The diagnostic composite scores are invariably based on a coagulation evaluation at a fixed point in time (e.g., at admission). A more continuous method might be helpful to enhance the diagnostic power of these scores employing routinely available markers in consumption coagulopathies. In the ISTH score for less severe DIC, some tests have to be performed multiple times, and amelioration of one or more of these assays results in negative points. This ‘inclination’ scoring makes continuous evaluation of (imminent) DIC possible and maybe helpful to assess the effect of therapeutic interventions over time [51]. In a validation study in more than 800 patients, progression of coagulation abnormalities after admission was associated with progressive organ dysfunction and impaired survival in critically ill patients [52]. Coagulation abnormalities such as sustained prolongation of PT and platelets were strongly predictive for development of multiple organ dysfunction, impaired improvement of organ dysfunction, and 28-day risk of death. Combining this algorithm to APACHE-II more strongly forecasted development of multiple organ dysfunction.

ADJUNCTIVE TREATMENT OF DIC

State of the art treatment of patients with consumption coagulopathies is based on forceful management of the precipitating condition. However, adjunctive strategies may be required to ameliorate the coagulopathy and supplement supportive care [53].

Transfusional options

Thrombocytopenia and clotting factor deficiency may predispose for major hemorrhagic complications. Nevertheless, transfusion of plasma or platelets should not be prescribed based on laboratory tests only. This treatment option should be reserved for patients with active hemorrhage or scheduled to undergo an operation or intervention associated with bleeding or patients who have a high chance of hemorrhagic events [2]. The supposed benefit of transfusion of plasma, fibrinogen concentrate, cryoprecipitate, or platelets has never been established on methodologically sound intervention studies but is considered to be sensible options in patients with serious hemorrhage who have considerable hemostatic abnormalities. Transfusional strategies for low platelet counts usually consist of 1 or 2 units of platelet concentrate (five donors/unit) aiming to increase the platelet count to at least 20–30 × 10^9/L and in patients with active hemorrhage or scheduled for a high-risk intervention to at least 50 × 10^9/L.

Anticoagulant treatment

Anticoagulants to combat the hypercoagulability in DIC remain a matter of debate. Experimental investigations have demonstrated that heparin can to a certain extent block the hemostatic activation in DIC. Randomized clinical studies to confirm an advantage of heparin on clinically important parameters in DIC are not available. Theoretically, the safety of anticoagulant strategies in patients with consumption coagulopathies with a high hemorrhagic risk is debatable. A large randomized controlled study in patients with sepsis demonstrated a small benefit of heparin on mortality and did not show significant safety issues [54]. It is generally accepted that heparin is advantageous in patients with DIC due to specific clinical conditions such as metastasized malignancies, purpura fulminans, and major vascular abnormalities. In addition, heparin is effective for the treatment of thrombosis or embolic complications in patients with low grade sustained DIC. Lastly, and importantly, all relevant guidelines advocate the administration of (low molecular weight) heparin prophylaxis for the prevention of venous thromboembolism in ICU patients [2].

A new therapeutic agent that is currently under evaluation is human soluble thrombomodulin that is produced through recombinant techniques. As mentioned before, thrombin binds to this molecule, which will then convert protein C into active protein C. In view of the central role of the protein C pathway in the pathogenesis of DIC, soluble thrombomodulin can be regarded as a promising candidate adjunctive drug in DIC [55]. In an initial controlled clinical study in patients with sepsis-associated coagulopathy, recombinant thrombomodulin was shown to markedly ameliorate the hemorrhagic complications and laboratory markers compared with conventional anticoagulation. At present, confirmatory studies with this agent are executed and designed to assess the potential role of soluble thrombomodulin on coagulation abnormalities, organ dysfunction, and survival in critically ill patients.

Infusion of physiological anticoagulants

In view of the exhaustion of relevant physiological anticoagulant systems and their role in the pathogenesis of consumption coagulopathies, normalization of the levels of these factors may be theoretically justified. In initial clinical studies, administration of supraphysiological dosages of antithrombin was associated with a small, albeit nonsignificant survival benefit. An adequately powered, international, controlled clinical study in septic patients could not demonstrate a significant survival advantage in the antithrombin group and a post hoc analysis of all clinical studies with antithrombin also showed no decrease in the risk of death. However, a small but consistent (1.5-fold) increase in the risk of hemorrhage was seen in patients treated with antithrombin [56]. Of note, retrospective subcategory analyses of the studies point to a significant advantage of antithrombin treatment in patients not on heparin and with a high DIC score in the aforementioned composite scoring systems, but this finding awaits confirmation in prospective trials.

A controlled clinical study in septic patients with activated protein C (APC), produced through recombinant technology, demonstrated a reduction in 28-day mortality [21]. Again, patients who had the most severe DIC had a relatively large treatment benefit compared with patient with no or only mild hemostatic abnormalities [49]. Additional studies with recombinant-activated protein C could not confirm, however, the efficacy of this approach and also some safety issues (mainly bleeding complications) were raised. A recent study in critically ill patients with septic shock did not show any advantage of activated protein C compared with placebo [57]. Consequently, this agent has been removed from the market, and relevant clinical guidelines for treatment of hemostatic abnormalities in critically ill patients have been revised [58].

CONCLUSION

Disseminated intravascular coagulation is often regarded as a complex clinical condition that is difficult to diagnose in the absence of adequate and accurate laboratory tests. Indeed, there is no assay that in itself can ascertain or discard a diagnosis of DIC but composite scoring systems employing routinely available clotting assays have shown to be valid for confirming this diagnosis. The international DIC scoring system combines results from the number of platelets, the PT or INR, and an assay for fibrin degradation products, and not only provides a simple tool for the diagnosis of DIC but has also strong prognostic power. Novel or renewed bedside tests are becoming increasingly available but may need more clinical evaluation before their use can be advocated. Dynamic monitoring of clotting tests may further improve the diagnosis and monitoring of specific treatment. Current insights into the pathophysiology of consumptive coagulopathies have led to new treatment options, directed at the attenuation of thrombin generation or regulation of coagulation activation. However, the clinical benefit of these strategies has not yet been firmly established so far.

REFERENCES

1. Levi M, ten Cate H. Disseminated intravascular coagulation. N Engl J Med 1999;341: 586–92.
2. Levi M, Toh CH, Thachil J, Watson HG. Guidelines for the diagnosis and management of disseminated intravascular coagulation. British Committee for Standards in Haematology. Br J Haematol 2009;145:24–33.
3. Levi M, Meijers JC. DIC: which laboratory tests are most useful. Blood Rev 2011;25: 33–7.
4. Levi M, van der Poll T, Schultz M. New insights into pathways that determine the link between infection and thrombosis. Neth J Med 2012;70:114–20.
5. Vanderschueren S, De Weerdt A, Malbrain M, Vankersschaever D, Frans E, Wilmer A, Bobbaers H. Thrombocytopenia and prognosis in intensive care. Crit Care Med 2000;28:1871–6.
6. Strauss R, Wehler M, Mehler K, Kreutzer D, Koebnick C, Hahn EG. Thrombocytopenia in patients in the medical intensive care unit: bleeding prevalence, transfusion requirements, and outcome. Crit Care Med 2002;30:1765–71.
7. Stephan F, Hollande J, Richard O, Cheffi A, Maier-Redelsperger M, Flahault A. Thrombocytopenia in a surgical ICU. Chest 1999; 115:1363–70.
8. Akca S, Haji Michael P, de Medonca A, Suter PM, Levi M, Vincent JL. The time course of platelet counts in critically ill patients. Crit Care Med 2002;30:753–6.
9. Levi M, Opal SM. Coagulation abnormalities in critically ill patients. Crit Care 2006;10:222.
10. MacLeod JB, Lynn M, McKenney MG, Cohn SM, Murtha M. Early coagulopathy predicts mortality in trauma. J Trauma 2003;55:39–44.
11. Greaves M, Preston FE. Approach to the bleeding patient. In: Hemostasis and Thrombosis. Basic Principles and Clinical Practice, 4th edn. Colman RW, Hirsh J, Marder VJ, Clowes AW, George JN (eds). Philadelphia: Lippingcott William & Wilkins; 2001: 1031–43.
12. Kitchen S, Preston FE. Standardization of prothrombin time for laboratory control of oral anticoagulant therapy. Semin Thromb Hemost 1999;25:17–25.
13. Keeling D. International Normalized Ratio in patients not on vitamin K antagonists. J Thromb Haemost 2007;5:188–9.
14. Lowenberg EC, Meijers JC, Levi M. Platelet-vessel wall interaction in health and disease. Neth J Med 2010;68:242–51.
15. Bakhtiari K, Meijers JC, de Jonge E, Levi M. Prospective validation of the international society of thrombosis and haemostasis scoring system for disseminated intravascular coagulation. Crit Care Med 2004;32:2416–21.
16. Dempfle CE. The use of soluble fibrin in evaluating the acute and chronic hypercoagulable state. Thromb Haemost 1999; 82:673–83.
17. McCarron BI, Marder VJ, Kanouse JJ, Francis CW. A soluble fibrin standard: comparable dose-response with immunologic and functional assays. Thromb Haemost 1999;82:145–8.
18. Westerlund E, Woodhams BJ, Eintrei J, Soderblom L, Antovic JP. The evaluation of two automated soluble fibrin assays for use in the routine hospital laboratory. Int J Lab Hematol 2013;35:666–71.
19. Hatada T, Wada H, Kawasugi K, Okamoto K, Uchiyama T, Kushimoto S, Seki Y, Okamura T, Imai H, Kaneko T, Nobori T. Analysis of the cutoff values in fibrin-related markers for the diagnosis of overt DIC. Clin Appl Thromb Hemost 2012;18:495–500.
20. Shorr AF, Thomas SJ, Alkins SA, Fitzpatrick TM, Ling GS. D-dimer correlates with proinflammatory cytokine levels and outcomes in critically ill patients. Chest 2002;121:1262–8.
21. Bernard GR, Vincent JL, Laterre PF, LaRosa SP, Dhainaut JF, Lopez-Rodriguez A, Steingrub JS, Garber GE, Helterbrand JD, Ely EW, Fisher CJJ. Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med 2001;344:699–709.
22. Boisclair MD, Ireland H, Lane DA. Assessment of hypercoagulable states by measurement of activation fragments and peptides. [Review] [113 refs]. Blood Rev 1990;4:25–40.
23. Gando S, Nanzaki S, Sasaki S, Kemmotsu O. Significant correlations between tissue factor and thrombin markers in trauma and septic patients with disseminated intravascular coagulation. Thromb Haemost 1998;79:1111–5.
24. Seitz R, Wolf M, Egbring R, Havemann K. The disturbance of hemostasis in septic shock: role of neutrophil elastase and thrombin, effects of antithrombin III and plasma substitution. Eur J Haematol 1989; 43:22–8.
25. Fijnvandraat K, Derkx B, Peters M, Bijlmer R, Sturk A, Prins MH, van Deventer SJ, ten Cate JW. Coagulation activation and tissue necrosis in meningococcal septic shock: severely reduced protein C levels predict a high mortality. Thromb Haemost 1995;73:15–20.
26. Bajzar L, Morser J, Nesheim M. TAFI, or plasma procarboxypeptidase B, couples the

coagulation and fibrinolytic cascades through the thrombin-thrombomodulin complex. J Biol Chem 1996;271:16603–8.

27. Taylor FB Jr, Peer GT, Lockhart MS, Ferrell G, Esmon CT. Endothelial cell protein C receptor plays an important role in protein C activation *in vivo*. Blood 2001;97:1685–8.
28. Faust SN, Levin M, Harrison OB, Goldin RD, Lockhart MS, Kondaveeti S, Laszik Z, Esmon CT, Heyderman RS. Dysfunction of endothelial protein C activation in severe meningococcal sepsis. N Engl J Med 2001;345:408–16.
29. Schouten M, van 't Veer C, van der Poll T, Levi M. Effect of the factor V Leiden mutation on the incidence and outcome of severe infection and sepsis. Neth J Med 2012;70:306–10.
30. Novotny WF, Brown SG, Miletich JP, Rader DJ, Broze GJ Jr. Plasma antigen levels of the lipoprotein-associated coagulation inhibitor in patient samples. Blood 1991;78:387–93.
31. Gando S, Kameue T, Morimoto Y, Matsuda M, Hayakawa M, Kemmotsu O. Tissue factor production not balanced by tissue factor pathway inhibitor in sepsis promotes poor prognosis. Crit Care Med 2002;30:1729–34.
32. Biemond BJ, Levi M, ten Cate H, van der Poll T, Buller HR, Hack CE, ten Cate J. Plasminogen activator and plasminogen activator inhibitor I release during experimental endotoxaemia in chimpanzees: effect of interventions in the cytokine and coagulation cascades. Clin Sci (Colch) 1995;88:587–94.
33. Levi M, Roem D, Kamp AM, de Boer J, Hack CE, ten Cate J. Assessment of the relative contribution of different protease inhibitors to the inhibition of plasmin *in vivo*. Thromb Haemost 1993;69:141–6.
34. Levi M, de Boer J, Roem D, ten Cate J, Hack CE. Plasminogen activation *in vivo* upon intravenous infusion of DDAVP. Quantitative assessment of plasmin-alpha 2-antiplasmin complex with a novel monoclonal antibody based radioimmunoassay. Thromb Haemost 1992;67:111–6.
35. Mesters RM, Florke N, Ostermann H, Kienast J. Increase of plasminogen activator inhibitor levels predicts outcome of leukocytopenic patients with sepsis. Thromb Haemost 1996;75:902–7.
36. Hermans PW, Hibberd ML, Booy R, Daramola O, Hazelzet JA, de Groot R, Levin M. 4G/5G promoter polymorphism in the plasminogen-activator-inhibitor-1 gene and outcome of meningococcal disease. Meningococcal Research Group. Lancet 1999;354:556–60.
37. Nossel HL, Yudelman I, Canfield RE, Butler VPJ, Spanondis K, Wilner GD, Qureshi GD. Measurement of fibrinopeptide A in human blood. J Clin Invest 1974;54:43–53.
38. Dempfle CE, Borggrefe M. Point of care coagulation tests in critically ill patients. Semin Thromb Hemost 2008;34:445–50.
39. Johansson PI, Stensballe J, Vindelov N, Perner A, Espersen K. Hypocoagulability, as evaluated by thrombelastography, at admission to the ICU is associated with increased 30-day mortality. Blood Coagul Fibrinolysis 2010;21:168–74.
40. Park MS, Martini WZ, Dubick MA, Salinas J, Butenas S, Kheirabadi BS, Pusateri AE, Vos JA, Guymon CH, Wolf SE, Mann KG, Holcomb JB. Thromboelastography as a better indicator of hypercoagulable state after injury than prothrombin time or activated partial thromboplastin time. J Trauma 2009;67:266–75.
41. Collins PW, Macchiavello LI, Lewis SJ, Macartney NJ, Saayman AG, Luddington R, Baglin T, Findlay GP. Global tests of haemostasis in critically ill patients with severe sepsis syndrome compared to controls. Br J Haematol 2006;135:220–7.
42. Taylor FBJ, Toh CH, Hoots WK, Wada H, Levi M. Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. Thromb Haemost 2001;86:1327–30.
43. Wada H, Hatada T, Okamoto K, Uchiyama T, Kawasugi K, Mayumi T, Gando S, Kushimoto S, Seki Y, Madoiwa S, Okamura T, Toc CH. Modified non-overt DIC diagnostic criteria predict the early phase of overt-DIC. Am J Hematol 2010;85:691–4.
44. Kim HK, Hong KH, Toh CH. Application of the international normalized ratio in the scoring system for disseminated intravascular coagulation. J Thromb Haemost 2010;8:1116–8.
45. Horan JT, Francis CW. Fibrin degradation products, fibrin monomer and soluble fibrin in disseminated intravascular coagulation. Semin Thromb Hemost 2001;27:657–66.
46. Toh CH, Hoots WK. The scoring system of the Scientific and Standardisation Committee on Disseminated Intravascular Coagulation of the International Society on Thrombosis and Haemostasis: a five year overview. J Thromb Haemost 2007;5:604–6.
47. Levi M. Disseminated intravascular coagulation in cancer patients. Best Pract Res Clin Haematol 2009;22:129–36.
48. Thachil J, Toh CH. Disseminated intravascular coagulation in obstetric disorders and its acute haematological management. Blood Rev 2009;23:167–76.
49. Dhainaut JF, Yan SB, Joyce DE, Pettila V, Basson BR, Brandt JT, Sundin D, Levi M. Treatment effects of drotrecogin alfa (activated) in patients with severe sepsis with or without overt disseminated intravascular coagulation. J Thromb Haemost 2004;2:1924–33.
50. Wada H, Gabazza EC, Asakura H, Koike K, Okamoto K, Maruyama I, Shiku H, Nobori T. Comparison of diagnostic criteria for disseminated intravascular coagulation (DIC): diagnostic criteria of the International Society of Thrombosis and Hemostasis and of the Japanese Ministry of Health and Welfare for overt DIC. Am J Hematol 2003;74:17–22.
51. Dhainaut JF, Shorr AF, Macias WL, Kollef MJ, Levi M, Reinhart K, Nelson DR. Dynamic evolution of coagulopathy in the first day of severe sepsis: relationship with mortality and organ failure. Crit Care Med 2005;33:341–8.
52. Kinasewitz GT, Zein JG, Lee GL, Nazir SR, Taylor FB Jr. Prognostic value of a simple evolving DIC score in patients with severe sepsis. Crit Care Med 2005;33:2214–21.
53. Levi M, van der Poll T. Disseminated intravascular coagulation: a review for the internist. Intern Emerg Med 2013;8:23–32.
54. Levi M, Levy M, Williams MD, Douglas I, Artigas A, Antonelli M, Wyncoll D, Janes J, Booth FV, Wang D, Sundin DP, Macias WL. Prophylactic heparin in patients with severe sepsis treated with drotrecogin alfa (activated). Am J Respir Crit Care Med 2007;176:483–90.
55. Levi M, van der Poll T. Thrombomodulin in sepsis. Minerva Anestesiol 2013;79:294–8.
56. Warren BL, Eid A, Singer P, Pillay SS, Carl P, Novak I, Chalupa P, Atherstone A, Penzes I, Kubler A, Knaub S, Keinecke HO, Heinrichs H, Schindel F, Juers M, Bone RC, Opal SM. Caring for the critically ill patient. High-dose antithrombin III in severe sepsis: a randomized controlled trial. JAMA 2001;286:1869–78.
57. Ranieri VM, Thompson BT, Barie PS, Dhainaut JF, Douglas IS, Finfer S, Gårdlund B, Marshall JC, Rhodes A, Artigas A, Payen D, Tenhunen J, Al-Khalidi HR, Thompson V, Janes J, Macias WL, Vangerow B, Williams MD. Drotrecogin alfa (activated) in adults with septic shock. N Engl J Med 2012;366:2055–64.
58. Thachil J, Toh CH, Levi M, Watson HG. The withdrawal of Activated Protein C from the use in patients with severe sepsis and DIC [Amendment to the BCSH guideline on disseminated intravascular coagulation]. Br J Haematol 2012;157:493–4.